Editor's LETTER

ACS chemical biology

Decoding Signals with Chemical Biology

A hallmark of living organisms is their ability to respond to information in their environment. Individual cells can detect signals (typically molecules) that elicit phenotypic changes. The term for this biological information processing, signal transduction, was coined by Rodbell over 40 years ago (*1*), and it is the topic of this special issue. Advances in signal transduction have been fueled by researchers whose interests and insights transcend traditional boundaries. The groundwork for understanding the underlying molecular mechanisms was laid about 130 years ago (*ca.* 1880), when Ehrlich and Langley independently postulated that cellular responses could be altered by the interaction of compounds with receptors (*2*). There is a long history in pharmacology of using ligands that either activate or block specific receptors to probe receptor function. More recently, the alliance between chemistry and biology is providing the means to further explore and exploit signal transduction pathways. In the first 2010 issue of *ACS Chemical Biology*, we have collected review articles that pay homage to this history by highlighting research at the frontiers of signal transduction.

A signaling pathway can be activated by an appropriate ligand (signal) when it binds to an intracellular or an extracellular receptor. In either case, ligand binding sets off a cascade of events, including the production of second messengers and changes in macromolecular interactions within the cell. The molecular mechanisms by which a receptor–ligand binding event can elicit such complex changes is central to understanding and manipulating cellular and organismal responses. The review by Wasternack and Kombrink on jasmonate signaling provides an overview of how lipid-derived signals are generated and processed by plants. Jasmonates regulate numerous responses by their ability to influence gene expression, but how they do so has been mysterious. Although they target intracellular receptors like many hormones in animals (*e.g.*, steroid hormones), their mechanism-of-action differs. The review highlights the importance of jasmonate stereochemistry and the biosynthetic mechanisms that result in the production of this class of intriguing small molecule signals. It also presents the latest insights in jasmonate function. Recent results indicating these hormones influence ubiquitin-dependent proteolysis raise intriguing questions.

Most signaling pathways are initiated by receptor–ligand interactions that occur at the cell surface. The exterior of cells is coated with complex glycolipids and glycoproteins, which can activate or attenuate signaling pathways. The contribution by Parker and Kohler focuses on enzymes that influence signaling pathways through their ability to act on cell surface glycans. This aspect of glycan function remains relatively unexplored, rendering it ripe for the application of chemical biology approaches.

Methods to detect and monitor changes in the cell in response to signals can be transformative. Roger Tsien's introduction of Ca^{2+}-sensitive dyes is a notable example (*3*). Three reviews in this issue focus on monitoring changes in the concentration of key species within the cell. The contribution of Paulsen and Carroll offers insight into a critical second messenger in signal transduction, hydrogen peroxide. This compound, a member of the class of reactive oxygen species (ROS), influences signaling pathways through its oxidation of protein cysteine residues. New strategies to follow changes in cysteine oxidation state are described, as well as blueprints for using these approaches to illuminate the discrete molecular mechanisms by which ROS function in signaling. One means by which cysteine modification can affect signaling pathways is through alteration of protein phosphorylation levels.

10.1021/cb100006u CCC: $40.75 Published online January 15, 2010

Editor's LETTER

The widespread importance of protein phosphorylation in signaling provides impetus to develop technologies to monitor it. To this end, Grimsrud *et al.* offer a progress report on state-of-the-art advances in mass spectrometry for phosphoproteomics. The interdisciplinary approaches they describe are providing the means to quantify changes in the levels of all types of protein phosphorylation. The power of modern mass spectrometry also is a theme in the review by Vinayavekhin *et al.*, which focuses on metabolomics. Insight into how metabolic processes are perturbed in normal cell regulation and dysregulation may lead to new therapies for conditions ranging from infectious disease to cancer.

One powerful strategy to dissect signal transduction pathways is to use small molecules that elicit specific cellular phenotypes. This approach is often referred to as "chemical genetics", a term that suggests a relationship between the effects of small molecules and those resulting from gene inactivation or mutation (*4*). Small molecule ligands that alter signaling pathways have emerged as valuable probes for basic research and as tools to validate targets for drug discovery. The advantages and caveats of this tactic are described in four reviews that focus on very different biological systems. For example, small molecules can regulate gene expression by binding directly to RNA. The review by Topp and Gallivan describes how the function of these riboswitches can be co-opted to control cellular responses, including behavior. Atilla-Gokcumen *et al.* present examples of how small molecules can be used to investigate the fundamental cellular process of cytokinesis. This review underscores a key advantage of ligands: they can be used to exert temporal control over dynamic processes. The use of small molecules to probe biological pathways through phenotypic changes is also a theme in the review by Firestone and Chen. They provide an overview of small molecule modulators of developmental pathways and how they can used to control cell fate decisions. The ability to obtain and culture pluripotent cells offers new possibilities for drug discovery, cell-based therapies, and regenerative medicine. The strategies described, in which chemistry and chemical principles are used to elicit specific cell fate decisions, provide impetus for continued exploration of this exciting frontier. Krishnamurty and Maly discuss the importance of small molecule kinase inhibitors for cancer therapies and the molecular mechanisms that underlie drug resistance. Their contribution highlights the important therapeutic benefits of using small molecules to control signal transduction and how a molecular level understanding can overcome the challenges that arise.

In summary, we note that studies in chemical biology have made major contributions to understanding and manipulating signaling pathways. In addition to the review articles in this special issue, we have assembled a Thematic Signal Transduction Collection of select original articles from *ACS Chemical Biology* (http://pubs.acs.org/page/acbcct/thematic/signal-transduction.html). In this new year, we celebrate the past contributions of chemical biology to signaling and look forward to those come.

Laura L. Kiessling
Editor-in-Chief, *ACS Chemical Biology*

REFERENCES

1. Rubin, R. P. (2007) A brief history of great discoveries in pharmacology: In celebration of the centennial anniversary of the founding of the American Society of Pharmacology and Experimental Therapeutics, *Pharmacol. Rev. 59*, 289–359.
2. Maehle, A. H., Prull, C. R., and Halliwell, R. F. (2002) The emergence of the drug receptor theory, *Nat. Rev. Drug Discovery 1*, 637–641.
3. Tsien, R. Y. (1989) Fluorescent probes of cell signaling, *Annu. Rev. Biochem. 12*, 227–253.
4. Schreiber, S. L. (1998) Chemical genetics resulting from a passion for synthetic organic chemistry, *Biorg. Med. Chem. 6*, 1127–1152.